SERUM TRANSAMINASES IN 60 ASYMPTOMATIC OBESE WOMEN.

DISSERTATION SUBMITTED IN FULFILLMENT OF THE REGULATIONS FOR THE AWARD OF M.D. GENERAL MEDICINE.

DEPARTMENT OF GENERAL MEDICINE.
PSG INSTITUTE OF MEDICAL SCIENCES & RESEARCH
THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
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GUIDE

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CERTIFICATE

This is to certify that the thesis entitled SERUM TRANSAMINASES IN 60 ASYMPTOMATIC WOMEN is a bonafide work of Dr. G. R. MAHADEVAN, done under my direct guidance and supervision in the department of General medicine, PSG Institute of Medical Sciences & Research, Coimbatore in fulfillment of the regulations of Tamilnadu Dr. MGR Medical University for the award of MD degree in General Medicine.

GUIDE & HOD **PRINCIPAL**

DECLARATION

I hereby declare that this dissertation entitled SERUM TRANSAMINASES IN 60 ASYMPTOMATIC OBESE WOMEN was prepared by me under the direct guidance and supervision of Professor Dr. K. JAYACHANDRAN MD, PSG Institute of Medical Sciences & Research, Coimbatore.

The dissertation is submitted to the Tamilnadu Dr. MGR Medical University in fulfillment of the University regulations for the award of MD degree in General Medicine. This dissertation has not been submitted for the award of any other Degree or Diploma.

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INTRODUCTION :

Now that routine laboratory testing is automated and is frequently part of an annual health check up plans, physicians are often faced with the problem of a patient with one abnormal result on the measurement of serum Aminotransferases or Alkaline phosphatase but no symptoms. Many batteries of screening test now include measurement of serum Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase and Gamma-glutamyl transferase(1). Although these enzymes are present in many tissues through out the body, they are most often elevated in patients with liver disease and may reflect liver injury. The clinician should be aware of non-hepatic diseases that can cause abnormal liver enzymes, such as thyroid disorders and occult celiac disease. In those patients in which no explanation can be found at the time of the initial evaluation for these abnormal liver enzymes, there is a high probability of Nonalcoholic Fatty Liver Disease(NAFLD) due to obesity.

Several carefully conducted clinical studies, which included liver biopsy in all patients, have shown that most asymptomatic subjects with persistent liver tests abnormalities in the absence of specific biochemical markers or abnormal

imaging, have Nonalcoholic fatty liver disease(NAFLD)(2,3). Nonalcoholic fatty liver disease is the common explanation for abnormal liver function test results in blood donors, and it is the cause of asymptomatic elevation of Sr. Aminotransferase levels in upto 90% of cases once other causes of liver disease are excluded(3). Nonalcoholic Fatty liver disease is the most common cause of abnormal liver test results among adults in the United states. Obesity, Type 2 diabetes Mellitus, and dyslipidemia are co-existing conditions frequently associated with Nonalcoholic Fatty liver disease. The reported prevalence of obesity in several series of patients with NAFLD varied between 30 to 100 percent, the prevalence of type 2 diabetes varied between 10 and 70 percent, and the prevalence of dyslipidemia varied between 20 and 92 percent(4-19). Because Nonalcoholic Fatty liver disease is reversible, considerably by lifestyle interventions that also affect levels of established risk factors (such as regular exercise, strict glycaemic control and changing dietary habits), there is increasing interest in the causative factors and pathogenesis of this condition.

SERUM TRANSAMINASES

The serum transaminases are Aspartate aminotransferase (AST, Aspartate transaminase, Glutamate oxaloacetate transaminase) and Alanine aminotransferase (ALT, Alanine transaminase, Glutamate pyruvate transaminase)(20).

The serum transaminases are a group of enzymes that catalyse the interconversions of the aminoacids and alpha-oxoacids by transfer of amino groups.

CLINICAL SIGNIFICANCE

Transaminases are widely distributed in the human tissues. Both the transaminases are normally present in the human plasma, bile, cerebrospinal fluid and saliva, but none is detected in urine unless a kidney lesion is present.

Sr. AST is a mitochondrial enzyme present in large quantities in liver, heart, skeletal muscle and kidney and the Sr. AST levels increases whenever these tissues are acutely destroyed, presumably from damaged cells.(21)

Sr. ALT is a cytosolic enzyme also present in liver. Although the absolute quantity is less than Sr. AST, a greater proportion is present in liver compared to heart and skeletal muscle. An increase in Sr. ALT is therefore more specific for liver damage than Sr. AST. Hence these two

enzymes are important markers of liver injury and hence included in the liver function tests.(22,1)

Apart from Sr. AST and Sr. ALT, other components of liver function tests are Sr. Bilurubin(direct and indirect),Sr. Alkaline phosphatase,Sr. Gamma glutamate transferase, Sr. Albumin and Sr. Globulin. Prothrombin time is also an important marker showing the extent and severity of liver damage(1).

Both these enzymes are elevated in multiple diseased states and just not specific for one particular disease. For example, Sr. AST is elevated in myocardial infarction(23), other than the diseases of the liver. The Sr. Aminotrasferases levels are sensitive indicators of liver cell injury and are helpful in recognizing hepatocellular diseases such as hepatitis. Both the enzymes Sr. AST and Sr. ALT are released into blood in increasing amounts when the liver cell membrane is damaged. Necrosis of the liver cells are required for the release of the Aminotransferases. Infact there is poor correlation between the extent of liver damage and the level of Sr. Aminotransferases.

CAUSES OF CHRONICALLY ELEVATED TRANSAMINASES LEVELS(24)

HEPATIC CAUSES

1. **Alcohol abuse**
2. **Medication (See Box Below)**
3. **Chronic Hepatitis B and C**
4. **Steatosis and Nonalcoholic Fatty Liver Disease**
5. **Autoimmune hepatitis**
6. **Hemochromatosis**
7. **Wilson's disease**
8. **Alpha1 anti-trypsin deficiency**

NONHEPATIC CAUSES

1. **Celiac sprue**
2. **Inherited disorders of muscle metabolism**
3. **Strenuous exercise**

Common Agents That Can Cause Liver Transaminase Elevations Elevations	
Medications	Herbal supplements/vitamins
Acetaminophen	**Chaparral leaf**
Amiodarone	**Ephedra**
Amoxicillin- clavulanic acid	**Gentian**
Carbamazepine	**Germander**

Fluconazole	**Jin bu huan**
Glyburide	**Kava**
Heparin	**Scutellaria (skullcap)**
Isoniazid (INH)	**Senna**
Ketoconazole	**Shark cartilage**
Labetalol	**Vitamin A**
Nitrofurantoin	
Nonsteroidal anti-inflammatory drugs	
Phenytoin	
Protease inhibitors	
Sulfonamides	
Trazodone	
Information from reference (24).	

Chronic liver diseases linked with Sr. Aminotransferases:

1.Alcoholic liver disease and serum transaminases.

Excessive alcohol intake can lead to both acute and chronic liver injury. A mildly elevated level of serum aminotransferase with an AST-ALT ratio of 2:1 is highly suggestive of alcoholic liver injury. In one study (25), more than 90% of patients with an AST-ALT ratio of at least 2:1 had alcoholic liver disease, and more than 96% of patients with a ratio of at least 3:1 had alcoholic liver disease. Besides the AST-ALT ratio, an elevated Sr. GGT level is often useful in the diagnosis of

alcoholic liver disease. However, the liver response that regulates Sr. GGT levels in the body is extremely sensitive, and the level of Sr. GGT may become elevated with even moderate consumption of alcohol. The reported sensitivity of an elevated Sr. GGT level for the detection of alcohol ingestion is 52% to 94% (24).

Alcoholic liver disease ranges from fatty liver to alcoholic hepatitis to alcoholic cirrhosis. Patients with fatty liver and alcoholic hepatitis often experience remarkable reversal in liver histopathologic characteristics and clinical symptoms with alcohol cessation.

2. Hepatitis C and serum transaminases.

The diagnosis of hepatitis C is often made after routine measurement of liver enzymes reveals elevated levels. However, HCV infection may progress to decompensated cirrhosis and hepatocellular carcinoma in a significant proportion of patients. Known risk factors for HCV infection include blood transfusions before 1992 (before initiation of routine HCV antibody screening of the blood supply), injecting drug use, needle-stick injuries, long-term hemodialysis, and a history of

multiple sexual partners. Of these risk factors, injecting drug use carries the highest risk. A study of middle-class drug abusers in Rhode Island (27) determined that 76.7% of all patients who admitted to injecting drug use tested positive for HCV--an odds ratio of 22.6. Of persons exposed to HCV, 85% experience chronic infection. A positive HCV antibody test using a second-generation enzyme-linked immunosorbent assay (ELISA) in a person with risk factors for HCV usually suggests ongoing infection, although a confirmatory test is always recommended. In patients who deny the risk factors stated previously, the relatively inexpensive recombinant immunoblot assay (RIBA) might be a useful confirmatory test, since almost all persons with chronic infection have RIBA test results positive for HCV. However, in persons with one or more risk factors for HCV, a qualitative polymerase chain reaction test for detection of HCV RNA in serum is the recommended confirmatory(26,27).

3. Hepatitis B and serum transaminases.

In highly endemic areas, such as Asia and Africa, up to 15% of the population are long-term HBV carriers. The main routes of transmission in these areas are perinatal transmission (exposure to infected vaginal tract secretions and blood during labor) and horizontal transmission in childhood. The likelihood of chronic infection among

persons exposed to HBV is inversely related to age: up to 95% of those infected at an age less than 5 years have chronic HBV infection (28). The risk is especially great if a child's mother has active hepatitis B viral replication; moreover, the risk is directly proportional to her level of viremia. By comparison, the risk of chronic infection is less than 5% among adults exposed to this virus. In primary care clinics, neonatally acquired hepatitis B is generally detected through screening tests in high-risk patients, whereas adult-onset hepatitis B is often not detected until clinical signs of chronic liver disease develop. Serologic markers for HBV infection include hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), hepatitis B e antigen (HBeAg), and antibody to HBeAg (anti-HBe). Although these tests are helpful, serum HBV DNA testing is important to completely evaluate a patient with chronic HBV infection.

4*. Autoimmune hepatitis and serum transaminases.*

Autoimmune hepatitis should be included in the differential diagnosis of any patient with chronically elevated liver test results, particularly because autoimmune hepatitis is amenable to therapy.

Type 1 autoimmune hepatitis, the most common form, typically occurs in young to middle-aged women. The female-male ratio is 4:1. About 30% of patients present with acute symptoms and laboratory derangements, ranging from hyperbilirubinemia to striking elevations in levels of serum aminotransferase. Some patients with autoimmune hepatitis are asymptomatic and have only modest elevation of serum liver enzyme levels. There may be an association between autoimmune hepatitis and other autoimmune diseases, such as thyroiditis and rheumatoid arthritis (24).

The diagnosis of autoimmune hepatitis is suggested by serum tests that are positive for antinuclear antibodies, anti-smooth muscle antibodies, or hypergammaglobulinemia (an elevated gamma-globulin fraction on serum protein electrophoresis). A liver biopsy showing periportal inflammation, interface hepatitis, increased bridging necrosis, and diffuse infiltration of predominantly plasma cells confirms the diagnosis.

5. Hemochromatosis and serum transaminases.

Hereditary hemochromatosis is an autosomal recessive condition that primarily affects persons of Northern European ancestry. Hereditary hemochromatosis is characterized by excessive gastrointestinal absorption of iron from a normal diet and subsequent iron deposition in

the liver, heart, pancreas, anterior pituitary, skin, and joints. Although women may experience all the manifestations of iron overload, the degree of iron loading is usually lower in women than in men because of physiologic blood loss from menstruation.

Elevated Sr. Aminotransferase levels may prompt testing for hemochromatosis, but many patients, even those with marked iron overload, have normal liver enzyme levels. The diagnosis of hemochromatosis should be suspected in patients with elevated Sr. transferrin-iron saturation (>45%) or an elevated Sr. ferritin concentration (ferritin, >200 ng/mL in women, >300 ng/mL in men), or both. Liver biopsy findings include increased stainable iron in hepatocytes (rather than Kupffer cells) with the greatest density of iron in periportal rather than pericentral hepatocytes. A hepatic iron concentration greater than 4,000 micrograms/g of liver dry weight and a hepatic iron index (hepatic iron concentration divided by age in years) greater than 1.9 are useful to distinguish homozygotes from heterozygotes and to identify patients with alcoholic liver disease who have compensated liver disease (29). However, the hepatic iron concentration and hepatic iron index are not "gold standards" for the diagnosis of hereditary hemochromatosis. They may be low in homozygotes with mild or minimal phenotypic expression or high in

patients with end-stage liver disease who do not have hereditary hemochromatosis.

With the identification of the *HFE* gene mutation, the diagnosis of hereditary hemochromatosis can now be confirmed without a liver biopsy. Two *HFE* gene mutations were originally described: a "major" mutation involving a cysteine-to-tyrosine substitution at position 282 (C282Y) and a "minor" mutation involving a histidine-to-aspartate substitution at position 63 (H63D) mutations(30).

6. Simple steatosis and nonalcoholic steatohepatitis.

Nonalcoholic fatty liver disease comprises a spectrum from steatosis to NASH. The term *simple steatosis* is used to describe fatty deposition in the liver without the necroinflammatory changes or fibrosis, or both, that are present in NASH. Although steatosis and NASH may be associated with elevated Sr. Aminotransferase levels, the natural history in these two entities is thought to be different. Steatosis is generally considered a benign and nonprogressive condition, whereas NASH may be associated with progressive injury that leads to fibrosis and cirrhosis in some patients. The most common risk factors for NASH include obesity (body mass index, ≥30), type 2 diabetes mellitus, hypertriglyceridemia, use of a variety of medications or toxins, and jejunoileal bypass (31).

A detailed alcohol history needs to be obtained before a diagnosis of NASH is considered, because NASH may be histologically indistinguishable from Alcoholic liver disease. Serum levels of AST and ALT may aid the physician in differentiating NASH from alcoholic liver disease, because patients with NASH usually do not have a greatly increased AST-ALT ratio. Although imaging studies such as ultrasound or computed tomography may suggest fatty infiltration of the liver, a biopsy is necessary to definitively establish the diagnosis.

NASH is now recognized as a cause of cryptogenic cirrhosis, because there are no serologic markers for NASH and the characteristic findings of hepatic fatty infiltration and necroinflammation may disappear in late stages of the disease. Several recent studies (32,33) have found an increased prevalence of diabetes and obesity among patients with cryptogenic cirrhosis compared with patients who have cirrhosis from known causes. This evidence suggests that NASH may be an important etiologic factor in cryptogenic cirrhosis.

OBESITY AS A RISK FACTOR

Obesity and overweight are the most prevalent nutritional disorders among children and adults. Currently available data suggests that approximately 40% of children in the United States are overweight or obese, the prevalence of obesity is highest among

specific ethnic groups(34,35). Data regarding the Indian population is not available. Obesity predisposes to a number of metabolic disorders like insulin resistance, type II diabetes mellitus, hypertension, hyperlipidemia, liver and renal dysfunction, reproductive dysfunction and the most important coronary artery disease(36,37).

AIM OF THE STUDY

Obesity is the major cause of elevated Sr. Transaminases in asymptomatic subjects. Whether there is direct association between BMI and Sr. Transaminases is not clear. The aim of this study is to evaluate the Sr. Transaminase levels in 60 asymptomatic women, with simple obesity.

REVIEW OF LITERATURE

LIVER ENZYME TESTS

The battery of liver enzymes includes Alanine and Aspartate aminotransferases (ALT and AST), Alkaline phosphatase (ALP) and Gamma-glutamyltransferase (GGT)(1,38). Normal ranges are based on distributions from "healthy" volunteers. The upper limit of normal (ULN) is defined as the mean + 2 SD, which implies that 2.5% of the liver tests from these healthy persons exceed the ULN. The Sr. Aminotransferases catalyze the reversible transformation of á-ketoacids into amino acids. Their serum levels reflect the amount of hepatocellular injury and death on a day-by-day basis. Aminotransferases (and predominantly AST) are not only found in hepatocytes but also in other tissues (heart and skeletal muscles, kidney, brain, pancreas, lung, and red blood cells). The liver contains 400 U ALT/g protein (mainly cytoplasmic) and 500 U AST/g protein (>

803 % contained in mitochondria and endoplasmic reticulum). Damage to one gram of liver tissue (or the membranes of 171 million hepatocytes) results in a significant increase in the serum ALT activity. Sr. AST responds in the same fashion, especially following liver cell necrosis and destruction of mitochondria and endoplasmic reticulum. Alkaline phosphatase is found in the biliary pole of the hepatocytes, the bile duct epithelia, osteoblasts, kidney, lung, intestine and placenta. The serum activity present in normal individuals is predominantly due to the izoenzymes of the liver, bone and kidney. Thus, an isolated rise in Sr. ALP is seen in the third trimester of preganancy, during growth (bone Sr. ALP) or may be due to intestinal Sr. ALP (following ingestion of a fatty meal). In cholestatic liver disease, the elevated bile acids stimulate the synthesis of Sr. ALP. Differentiation between hepatic and non-hepatic causes of Sr. ALP elevation can be done by determination of Sr. ALP isoenzymes or more easily by testing for Sr. GGT, which rises in liver but not in bone disease. Sr. GGT is found in hepatocytes, cholangiocytes, kidney, pancreas, epididymis, heart, lung, intestine, bone marrow, salivary glands, thymus, spleen and brain, which is an explanation for the lack of specificity for the diagnosis of hepatobiliary disease. Elevated values of Sr. GGT are caused by damage to cellular membranes, cellular regeneration or by enhanced synthesis as a result of induction of the biotransformation enzyme system. Known inducers

are bile acids (cholestasis), prolonged regular abuse of alcohol and especially antiepileptic drugs (phenytoin, carbamazepine). A decline in Sr. GGT can be observed during oestrogen administration or pregnancy. Due to the sudden release of intracellular reservoirs of aminotransferases and their short halflife

(1 – 2 days), the levels of ALT and AST respond quickly to hepatocellular damage or acute bile duct obstruction. A rise in Sr. ALP and GGT occurs more slowly in response to cholestasis, and the levels are maintained longer due to a half-life of more than 4 days (41). Knowledge of these enzyme

kinetics is important for the correct interpretation of abnormal liver enzymes as predominant hepatocellular or cholestatic patterns.

PRINCIPLES OF DIAGNOSTIC ENZYMOLOGY

All of the hundreds of different enzymes present in the human body are synthesized intracellularly and most of them carry out their functions within the cells in which they are formed. However, certain enzymes are secreted, either in an active or inactive form and, after activation, function within the extracellular fluids. We are principally concerned with the changes in the activity of serum or plasma of the enzymes that are predominantly intracellular and that are normally present in the serum in low activities only. By measuring changes in

activities of these enzymes in disease, it is possible to infer the location and nature of pathological changes in tissues of body. Therefore it is necessary to understand the factors that affect the rate of release of enzymes from their cells of origin and the rate at which they are cleared from the circulation, so that changes in activity in disease can be interpreted correctly(38-41).

FACTORS AFFECTING ENZYME LEVELS IN PLASMA OR SERUM.

The measured level of activity of an enzyme in blood is the result of the balance between the rate at which it enters the circulation from its cells of origin and the rate at which it is inactivated or removed.

ENTRY OF ENZYMES INTO THE BLOOD

By far the most important factors that affect the enzyme activities in serum or plasma are those that influence the rate at which enzymes enter the circulation from the cells. These factors can be divided into two main categories: Those that affect the rates at which

enzymes leak from cells, and those that reflect altered rates of enzyme production, due either to increased synthesis of a particular enzyme by individual cell types or to proliferation of a particular type of enzyme producing cell.(38-41)

Leakage of enzymes from cells- **Enzymes are retained within their cells of origin by the plasma membrane surrounding the cell. The plasma membrane is a metabolically active part of the cell, and its integrity depends on the cell's energy production. Any process that impairs the energy production, either by depriving the cell of oxydizable substrates or restricting access of oxygen needed for energy production, will promote deterioration of the cell membrane. The membrane will become leaky and, if cellular injury becomes irreversible, the cell will die. Small molecules are the first to leak from damaged or dying cells followed by larger molecules such as enzymes; ultimately the whole contents of necrotic cells are discharged.**

Direct attack on the cell membranes by such agents as *viruses* or *organic chemicals* is an obvious cause of enzyme release and one that is particularly important in the case of the liver. A reduction in the supply of the oxygenated blood perfusing any tissue will promote enzyme release. The most obvious clinical condition in which such a reduction occurs is myocardial infarction(23). The cells of the affected

region rapidly begin to deteriorate and die, releasing their enzyme contents. Transfer of the enzymes to the extracellular fluids and lymphatics and then to the systemic circulation accounts for the rapid rise in serum enzyme activity that is characteristic of this condition. The liver is very sensitive to hypoxia, which can result from diminished cardiac output (heart failure). Increased activities of hepatocellular enzymes in the blood accompany a wide variety of conditions such as congestive heart failure, shock and hypoxia.

Because of the very high concentrations of enzymes within the cells, thousands or even ten-thousand times greater than the concentrations in extracellular fluid, and because of the sensitivity with which small amounts of enzyme can be detected by their catalytic activity, an increase of enzyme activity in the extracellular fluid or plasma is an extremely sensitive indicator of even minor cellular damage.

Enzyme changes reflecting altered enzyme production.

The small amounts of intracellular enzymes normally present in the plasma can be assumed to result from turn over of cells or leakage of enzymes from healthy cells. This contribution of enzymes to the circulating blood may decrease, either as a result of genetic deficiency of enzyme production or when enzyme production is depressed as a

result of disease. However, cases in which enzyme production is increased are of more general interest in diagnostic enzymology.

For example, an increase in the number and activity of the Alkaline phosphatase- producing osteoblast of bone is responsible for the increased level of the alkaline phosphatase in the serum of normally growing children. Increased osteoblastic activity also accounts for the increase levels of this enzyme in serum in various types of bone disease. Towards the end of normal pregnancy, the placenta constitutes a new source of Alkaline phosphatase and contributes its characteristic iso-enzyme to the maternal circulation.

Enzyme induction **may increase enzyme production; an example of such induction is the increased activity of Gamma glutamyl transferase in serum, which may result from the administration of drugs such as Barbiturates or Phenytoin and from intake of alcohol. Biliary obstruction causes increase synthesis of Alkaline phosphatase in the liver.**

CLEARANCE OF ENZYMES

Little is known about the way in which enzymes are cleared from the circulation from the circulation. Few enzyme molecules are small enough to pass through the healthy glomeruli of the kidney, and

therefore urinary excretion is not a major route for elimination of enzymes from the circulation. An exception to this is Amylase; increased levels of this enzyme in the blood (e.g. , following acute pancreatitis) are accompanied by increased excretion in the urine. Present evidence suggest that enzyme inactivation begins in the plasma and that inactivated enzymes are rapidly removed probably by the reticuloendothelial system. The half life (t 1/2) of an enzyme in plasma may be a few hours or several days, but in most cases an average half life of 24 to 48 hours can be expected(39,40).

The existence of circulating inhibitors or activators of enzymes has little effect on activities measured in the laboratory. When these inhibitors are of a reversible nature, the relatively high dilutions of serum used in most modern enzyme assays are sufficient to eliminate any possible effects from this cause.

THE SERUM TRANSAMINASES

1. **ASPARTATE TRANSAMINASE; ASPARTATE AMINOTRANSFERASE, (AST, GLUTAMATE OXALOACETATE TRANSAMINASE, GOT)**

2. **ALANINE TRANSAMINASE; ALANINE AMINOTRANSFERASE, (ALT, GLUTAMATE PYRUVATE TRANSAMINASE, GOT) (20)**

The aminotransferases are a group of enzymes that catalyse the interconversion of the amino acids and the alpha-oxy acids by transfer of amino groups. Distinct isoenzymes of aspartate transaminase are present in the cytoplasm and the mitochondria of cells. For example, in conditions associated with mild degree of liver tissue injury, the predominant isoenzyme form in serum is that from the cytoplasm. Although some mitochondrial isoenzymes is also present. Severe tissue damage results in the release of much mitochondrial isoenzyme as well.

The Alpha-oxoglutarate / L-glutamate couple serves as one amino group acceptor and donor pair in all amino-transfer reactions; the specificity of the individual of the individual enzymes derives from the particular amino acid that serves as the other donor od an amino

group. Thus Aspartate aminotransferase catalyses the reaction shown in the equation no (1).

(1) L-Aspartate + α-Oxoglutarate → Oxaloacetate + L-Glutamate

Alanine aminotransferase catalyses the analogous reaction presented in equation no: (2)

(2) L-Alanine + α-Oxoglutarate → Pyruvate + L-Glutamate

The reactions are reversible, but the equilibria of the AST and ALT reactions favour formation of Aspartate and Alanine respectively.

CLINICAL SIGNIFICANCE

The serum transaminases are widely distributed in human tissues. Both AST and ALT are normally present in human plasma, bile, cerebrospinal fluid and saliva but none is found in urine unless a kidney lesion is present.

In viral hepatitis and other forms of liver disease associated with hepatic necrosis, levels of Sr. AST and ALT are elevated even before clinical signs and symptoms of disease such as jaundice appear.

Activities of both enzymes may reach values as high as hundred times the upper reference limit, twenty to fifty fold elevations are most frequently encountered. Peak values of transaminase activity are seen between the seventh and twelfth days; values return to normal levels by the third to fifth week if recovery is uneventful. In toxic or viral hepatitis, ALT is characteristically as high as or higher than AST, and the ALT/AST ratio, which normally is <1, approaches or becomes greater than 1.

Moderately increased levels of AST and ALT activity may also be observed in extrahepatic cholestasis. Levels observed in cirrhosis vary with the status of the cirrhotic process; they range from upper normal to some 4-5 times normal, with the level of AST activity higher than that of ALT activity. Five to ten fold elevation of the two enzymes may occur in patients with primary or metastatic carcinoma of liver, with AST usually being higher than ALT, but levels are often normal in the early stages of malignant infiltration of liver. Slight or moderate elevations of both ALT and AST may be observed after intake of alcohol, during Delirium Tremens, and after administration of drugs such as opiates, salicylates, or ampicillin.

Although serum levels of both AST and ALT become elevated whenever disease process affect liver cell integrity, ALT is more liver

specific enzyme. Serum elevations of ALT activity are rarely observed in conditions other than parenchymal liver disease. Moreover, elevations of ALT activity persist longer than do those of AST activity.

Sensitivity and specificity of ALT for the detection of liver disease is around 83 % (42-44, 24). An isolated rise in ALT is of hepatocellular origin, after exclusion of macroenzyme-I-immune complexes. The diagnostic sensitivity of AST is significantly lower (70%) and less specific. The study of the AST: ALT ratio (or De-Rits ratio) can yield some additional information but specific etiologic diagnosis cannot usually be based on these routine tests or ratio's. In alcoholic liver disease the AST: ALT ratio is greater than 2:1, due to a alcohol-related deficiency of pyridoxal 5-phosphate (vitamin B6).

METHODS FOR THE MEASUREMENT OF TRANSAMINASES ACTIVITY

The assay system for measuring transaminase activity contains two amino acids and two oxo-acids as shown in equations (1) and (2). There is no convenient method for assaying either of the amino acids in the reaction system, therefore formation or consumption of the oxo-acids is measured(47).

TEST PRINCIPLE USED TO ESTIMATE SERUM AST LEVELS

The method is according to the International Federation of Clinical Chemistry (IFCC)(47). AST in the sample catalyses the transfer of an amino group between L-Aspartate and 2-oxoglutarate to form Oxaloacetate and L-Glutamate. The Oxaloacetate then reacts with NADH in the presence of Malate Dehydrogenase (MDH) , to form NAD^+.

(3) L-Aspartate + 2-Oxoglutarate $\rightleftharpoons$ Oxaloacetate + L-Glutamate

(4) Oxaloacetate + NADH + H^+ $\rightleftharpoons$ L-Malate + NAD^+

The rate of the NADH oxidation is directly proportional to the catalytic AST activity. It is determined by measuring the decrease in absorbance at 340nm(45,46).

TEST PRINCIPLE USED TO ESTIMATE SERUM ALT LEVELS

The method is according to the International Federation of Clinical Chemistry (IFCC)(47). ALT in the sample catalyses the transfer of an amino group between L-Alanine and 2-oxoglutarate to form Pyruvate and L-Glutamate. The Pyruvate formed is reduced by NADH in a reaction catalysed by Lactate Dehydrogenase (LDH) to form L-Lactate and NAD^+(48).

L-Alanine + 2-Oxoglutarate ⇌ Pyruvate + L-Glutamate

Pyruvate + NADH + H^+ ⇌ L-Lactate + NAD^+

The rate of the NADH oxidation is directly proportional to the catalytic ALT activity. It is determined by measuring the decrease in absorbance at 340nm(45,46).

REFERENCE RANGES(48)

1. ASPARTATE TRANSAMINASE

For MALES- UPTO 38 UNITS/L

For FEMALES- UPTO 32 UNITS/L

2. ALANINE TRANSAMINASE

For MALES- UPTO 41 UNITS/L

For FEMALES- UPTO 31UNITS/L

OBESITY;

DEFINITION- Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.

BODY MASS INDEX

Body mass index (BMI) is a simple index of weight-for-height that is commonly used in classifying overweight and obesity in adult populations and individuals. It is defined as the weight in kilograms divided by the square of the height in meters (kg/m2).

BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. However, it should be considered as a rough guide because it may not correspond to the same degree of fatness in different individuals.

The World Health Organization (WHO) defines "*overweight*" as a BMI equal to or more than 25, and "*obesity*" as a BMI equal to or more than 30 (37).

Waist Circumference and Waist to Hip Ratio

Determining waist circumference eliminates the inconsistencies of the BMI. Waist circumference measurement is an important part of determining obesity and morbid obesity. A waist circumference of 40 inches in men and 35 inches in women is an indication of obesity.

Waist to hip ratio is also used as a guideline for determining obesity. This measurement determines how weight is distributed on the body. Weight distribution on the lower half of the body (pear-

shape) generally does not pose the same serious consequences as weight that crowds the abdominal area. Hip to waist ratio is calculated by dividing the circumference of the waist by the circumference of the hips. A healthy waist to hip ratio for women is 0.80 or less. For men, 0.90 or less is a healthy waist to hip ratio. Anything over 1.0 is considered obese(49-52).

COMPLICATIONS OF OBESITY(53-55).

1. Insulin resistance and type II diabetes mellitus

2. Reproductive disorders

3. Hypertension

4. Dyslipidaemia

5. Cardiovascular disease

6. Obstructive sleep apnoea

7. Bone, joint and cutaneous disease

8. Non alcoholic fatty liver disease

9. Ovarian hyperandrogenism and gynaecomastia

10. Emotional and psychological sequalae

11. Focal glomerulosclerosis

12. Cholecystitis and gall stones

13. Polycystic ovarian syndrome

CLASSIFICATION OF OBESITY

WHO Classification	Popular Description	BMI (kg/m^2)	Risk of co-morbidities
Underweight	Thin	<18.5	Low (but risk of other clinical problems

			increased)
Normal range	Normal	18.5 - 24.9	Average
Overweight		> 25.0	
Pre-obese	Overweight	25 - 29.9	Increased
Obese Class I	Obese	30.0 - 34.9	Moderate
Obese Class II	Obese	35.0 - 39.9	Severe
Obese ClassIII	Morbidly Obese	> 40.0	Very severe

NOTE: In our study which was conducted between August 2006 – August 2008, we have included women with BMI of ≥ 30, considering a BMI ≥ 30 as obese according to WHO Obesity definition. In November 2008, India has released its revised BMI standards, specifically tailored for the Indian population. According to the Revised standards, BMI ≥ 23 is defined overweight and BMI ≥ 25 is defined obese.

ETIOLOGICAL CLASSIFICATION (56,37)

SIMPLE OBESITY

1. **Familial**

2. **Diet induced**

OBESITY DUE TO GENETIC SYNDROMES AND HORMONAL DISTURBANCES

1. **Downs syndrome**
2. **Turners syndrome**
3. **Cohens syndrome**
4. **Laurence Moon-Biedl syndrome**
5. **Pseudohypoparathyroidism**
6. **Prader Willi syndrome**
7. **Growth hormone deficiency**
8. **Growth hormone resistance**
9. **Hypothyroidism**
10. **Cushings syndrome**
11. **Precocious puberty**

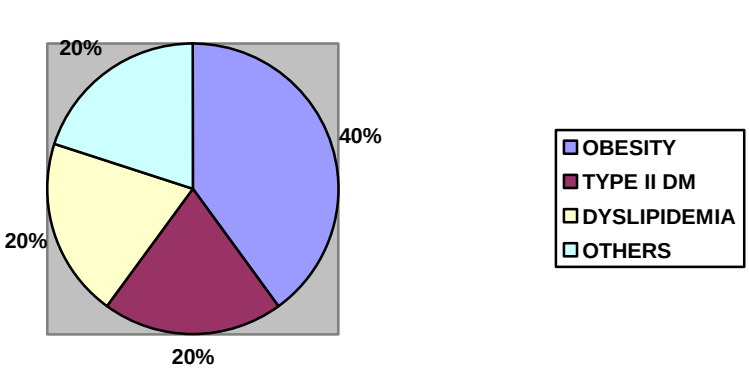
DRUG INDUCED OBESITY

1. **Cortisol and other Glucocorticoids**
2. **Tricyclic antidepressants**

3. **Monoamine oxidase inhibitors**
4. **Oral contraceptives**
5. **Insulin (in excessive doses)**
6. **Thiazolidinediones**
7. **Risperidone**
8. **Clozapine**

OBESITY AND NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic Fatty Liver disease (NAFLD) is an emerging clinical problem among obese subjects particularly those with central obesity. 40% of patients with NAFLD are overweight or obese, 20% have type 2 diabetes and 20% dyslipidemic(See Pie chart).



The development of the characteristic pathological changes within the liver are intimately related to the various clinical and

biological markers of the metabolic syndrome - BMI, waist circumference, hyperinsulinaemia, hypertriglyceridaemia, and impaired glucose tolerance. The diagnosis of NAFLD rests on characteristic histolological features that include substantial fat infiltration, necroinflammation and fibrosis in the absence of alcohol as a cause for the disease. In NAFLD the ratio of serum alanine transaminase (ALT) to aspartate transaminase (AST) is always >1 whereas the ratio in alcoholic liver disease is almost always <145. Histological evidence of fibrosis and/or cirrhosis is seen in up to 50% of patients with most patients, who initially show fibrosis, developing cirrhosis after 10 years - it has been suggested that "cryptogenic cirrhosis" represents "burnt out" NAFLD. A liver biopsy is necessary to make a diagnosis and is important for therapeutic and prognostic reasons - ultrasound scanning of the liver is not sufficiently sensitive to be diagnostic.

The causative factors inducing necrosis, inflammation and fibrosis within the liver include oxidative stress and subsequent lipid peroxidation, factors associated with abnormal cytokine production and factors associated with disordered fat metabolism and insulin resistance.

The two metabolic abnormalities most strongly associated with NAFLD are insulin resistance and an increase supply of free fatty acids to the liver (see section 2.1). There is evidence that NAFLD

associated with obesity and type 2 diabetes is due primarily to peripheral insulin resistance and consequential hyperinsulinaemia. Insulin blocks hepatic mitochondrial fatty acid oxidation and results in an increased concentration of intracellular fatty acids that may be directly toxic or lead to oxidative stress. The link between central obesity and liver injury may be explained by the fact that fatty acids are mobilised more rapidly from visceral (central) than subcutaneous fat and drain directly to the liver via the portal vein.

Weight loss is generally associated with a reduction in the severity of the biochemical abnormalities and a regression of the steatosis. Nevertheless, sudden weight loss or "weight cycling" (weight loss followed by weight regain) may predispose to NAFLD(57,58).

PATHOGENESIS(59-68)

It is not yet understood why simple steatosis develops in some patients with obesity, whereas steatohepatitis and progressive disease develops in others; differences in body-fat distribution or anti-oxidant systems, possibly in the context of a genetic predisposition, may be among the explanations.

A net retention of lipids within the hepatocytes, mostly in the form of triglycerides, is a prerequisite for the development of nonalcoholic fatty liver disease. The primary metabolic abnormalities

leading to lipid accumulation are not well understood, but they could consists of alterations in the pathways of uptake, synthesis, degradation, or secretion in hepatic lipid metabolism resulting from insulin resistance.

Insulin resistance is the most reproducible factor in the development of nonalcoholic fatty liver disease. The molecular pathogenesis of insulin resistance seems to be multifactorial, and several molecular targets involved in the inhibition of insulin action have been identified. These include Rad (ras

associated with diabetes), which interferes with essential cell functions (growth, differentiation, vesicular transport, and signal transduction); PC-1 (a membrane glycoprotein that has a role in insulin resistance), which reduces insulin-stimulated tyrosine kinase activity; leptin, which induces dephosphorylation of insulin-receptor substrate-1; fatty acids, which inhibit insulin-stimulated peripheral glucose uptake; and tumour necrosis factor, which down regulates insulin-induced phosphorylation of insulin receptor substrate-1 and reduces the expression of insulin dependant glucose-transport molecule Glu4. Insulin resistance leads to fat accumulation in the hepatocytes by two main mechanisms; lipolysis and dyslipidemia.

Clinically significant amounts of dicarboxylic acids, which are potentially cytotoxic, can be formed by microsomal oxidation. This pathway of fatty acid metabolism is closely related to mitochondrial oxidation and peroxisomal oxidation. Deficiency of the enzymes of peroxisomal oxidation has been recognized as an important cause of micro-vesicular steatosis and steatohepatitis. Deficiency of the acyl-coenzyme-A oxidase disrupts the oxidation of very-long-chain-fatty acids and diacryboxylic fatty acids, leading to extensive microvesicular steatosis and steatohepatitis. Loss of this enzyme also causes sustained hyperactivation of peroxisome-proliferator-activated receptor alpha, leading to transcriptional up-regulation of PPAR-alpha-regulated genes. PPAR-alpha has been implicated in promoting hepatic synthesis of uncoupling protein2, which is expressed in the liver of patients with nonalcoholic fatty liver disease.

Increased intrahepatic levels of fatty acids provide a source of oxidative stress, which may in large part be responsible for the progression from steatosis to steatohepatitis to cirrhosis. Mitochondria are the main cellular source of reactive oxygen species, which may trigger steatohepatitis and fibrosis by three main mechanisms: lipid peroxidation, cytokine induction, and induction of Fas ligand.

Patients with steatohepatitis have ultrastructural mitochondrial lesions, including linear crystalline inclusions in megamitochondria. This mitochondrial injury is absent in most patients with simple steatosis and in healthy subjects. Patients with steatohepatitis slowly resynthesize ATP in vivo after a fructose challenge, which causes acute hepatic ATP depletion. This impaired ATP recovery may reflect the mitochondrial injury found in patients with steatohepatitis.

Thus although symptoms are liver disease develop rarely in patients with fatty liver who are obese, the steatotic liver may be vulnerable to further injury when challenged by additional insults. This has led to the presumption that progression from simple steatosis to steatohepatitis and to advanced fibrosis results from two distinct events. First, insulin resistance leads to accumulation of fat within hepatocytes, and second, mitochondrial reactive oxygen species cause lipid peroxidation, cytokine induction, and the induction of Fas ligand.

IMAGING STUDIES

On ultrasonography, fatty infiltration of the liver produces a diffuse increase in echogenecity as compared with that of the kidneys. Regardless of the cause, cirrhosis has similar appearance on ultrasonography. Ultrasonography has a sensitivity of 89% and a specificity of 93% in detecting steatosis and a sensitivity and

specificity of 77% and 89%, respectively, in detecting increased fibrosis.(69)

Fatty infiltration of the liver produces a low density hepatic parenchyma on computed tomographic (CT) scanning. Steatosis is diffuse in most patients with nonalcoholic fatty liver disease, but occasionally it is focal. Consequently, ultrasonography and CT scans may be misinterpreted as showing malignant liver masses(70). In such cases, magnetic resonance imaging can distinguish space occupying lesions from focal fatty infiltration (characterized by isolated areas of fat infiltration) or focal fatty sparing (characterized by isolated areas of fatty liver)(71). Magnetic resonance spectroscopy allows a quantitative assessment of fatty infiltration of liver due to obesity or any other cause(72).

MATERIALS AND METHODS;

This study was carried out in *60 ASYPMTOMATIC OBESE WOMEN* who

came for routine MASTER HEALTH CHECK UP between August 2006 and August 2008, in PSG Hospitals, Coimbatore.

Women subjects were primarily chosen, to rule out alcohol as a causative factor, for the changes in levels of serum transaminases.

All patients were screened according to a protocol consisting of a complete medical history, medical examination, BMI, Waist circumference, Liver function tests, other standardized blood tests, Ultrasonography of the abdomen.

Obesity **was defined as a Body mass index (weight in kilograms divided by square of his or her height in metres) of 30 or more.**

Routine laboratory investigations included a complete blood count, erythrocyte sedimentation rate, urea, creatinine, Fasting and post prandial blood glucose, Fasting total cholesterol, and Liver function tests. Other investigations included ECG, Chest X-ray.

TOTAL CHOLESTEROL VALUES

TOTAL CHOLESTEROL	
<200 (5.17)	**Desirable**
200 – 239 (5.17-6.18)	**Borderline high**
≥240 (≥6.21)	**High**

Serum Transaminases were estimated using IFCC () methods using COBAS INTEGRA DEVICE(47).

Analyses were adjusted for the effects of age at screening, BMI, total cholesterol level or the presence or absence of fatty liver in Ultrasonography of the abdomen.

EXCLUSION CRITERIA ;

1. **Diabetes Mellitus Type I or type II.**
2. **Pre-existing or present evidence of liver or kidney or cardiac disease.**
3. **Pregnant women.**
4. **Patients on any drugs that impair the liver function.**
5. **History or evidence of any endocrine disorders.**
6. **History or evidence of any hormonal disturbances.**
7. **History of alcohol use.**
8. **History of fever or hospital admissions recently.**

Determination of Serum Transaminase levels;

Blood was drawn as fasting samples participants into heparinised tubes.

Serum transaminases were estimated by the automated device (COBAS

INTEGRA) . Reference ranges for *Aspartate transaminase* was up to 32 U/L

and *Alanine transaminase* was up to 31 U/L in females in our laboratory(48).

Statistical analysis ;

It was perfomed using SPSS PC 11.5. Analysis was performed to find

the effect of each variable.

PROFORMA

Sr. AST and ALT levels in asymptomatic obese women

Name : **Age:** **Address:**

OP.No : **Sex:**

Presenting complaints if any:

Significant Past History :

- **Diabetes Mellitus**
- **Dyslipidemia or any drugs for dyslipidemia**
- **Hypertension**
- **Pre-existing Liver disease**
- **Jaundice**
- **Renal disease**
- **Parenteral nutrition**
- **Heart disease**
- **Coronary artery disease**
- **Hypothyroidism**
- **Cushings syndrome or Pseudo Cushings syndrome**
- **Any other genetic syndromes**
- **Hormonal disturbances**

- **Emotional disturbances**
- **Blood or Blood products transfusion**

Personal history :

- **eating habits**
- **sleep pattern smoking**
- **alcohol**

Any previous hospital admissions:

History of any drug intake:

O/e

General Physical Examination : -

Pallor : Yes / No **Cyanosis : Yes / No**

Clubbing : Yes / No **Pedal Edema : Yes / No**

Pulse:- / min

BP : / mm hg

Height: **BMI:**

Weight: **Waist circumference:**

INVESTIGATIONS :-

COMPLETE BLOOD COUNT:

Hb

RBC

WBC

Platelets

ESR

Sr. Urea

Sr. Creatinine

Fasting blood glucose

Post prandial blood glucose

Urine examination

Fasting Total cholesterol:

Sr. AST :-

Sr. ALT :-

CXR :

ECG :

ULTRASOUND OF ABDOMEN:

Inference :-

RESULTS

SERUM TRANSAMINASE LEVELS IN STUDY SUBJECTS

NO	*AGE*	*BMI*	*AST*	*ALT*	*TOTAL CHOL*	*FATTY LIVER*
1.	37	30.4	45	47	254	P
2.	43	32.3	41	39	239	P
3.	64	31	56	49	247	P
4.	47	31.6	21	18	156	A
5.	37	32.4	66	111	272	P
6.	47	30.8	31	42	200	P
7.	45	31	27	28	192	A
8.	59	31.4	88	67	265	P
9.	41	32	78	98	234	P
10.	53	30.7	59	65	311	P
11.	52	30.6	48	57	289	P
12.	51	31.8	20	31	212	A
13.	35	32.8	61	47	323	P
14.	31	30.1	31	37	278	P
15.	43	30	39	56	167	A

S.NO	AGE	BMI	AST	ALT	TOTAL CHOL	FATTY LIVER
16.	64	31.1	41	33	222	P
17.	35	32.4	39	56	256	P
18.	47	30.2	18	43	250	A
19.	39	31.5	50	57	198	P
20.	56	32.6	76	34	244	P
21.	33	31.8	46	79	264	P
22.	62	30.4	34	44	260	P
23.	57	33.8	22	18	240	P
24.	49	31.6	80	112	257	P
25.	39	32.7	33	48	215	P
26.	41	31.5	26	33	178	A
27.	50	32.8	64	59	259	A
28.	22	30.6	21	18	190	P
29.	61	31.4	120	79	278	P
30.	36	31.8	50	68	299	P
31.	47	32.3	23	26	232	A
32.	55	30.6	66	45	343	P
33.	38	32.6	74	63	287	P

S.NO	AGE	BMI	AST	ALT	TOTAL CHOL	FATTY LIVER
34.	58	30.7	77	48	181	P
35.	34	32.2	35	36	231	A
36.	68	31.8	48	90	276	P
37.	40	32	64	63	320	P
38.	31	31	20	24	152	A
39.	58	31.7	31	18	260	A
40.	51	30.9	47	39	282	A
41.	29	31.6	50	41	194	P
42.	39	30.8	18	22	123	A
43.	53	30.1	39	58	254	P
44.	63	32.7	44	68	324	P
45.	50	33	74	66	259	P
46.	45	32.8	40	66	239	P
47.	53	30.6	87	50	257	A
48.	37	31	17	22	219	A
49.	35	33.4	60	142	183	P
50.	55	31.7	33	34	240	A

S.NO	*AGE*	*BMI*	*AST*	*ALT*	*TOTAL CHOL*	*FATTY LIVER*
51.	28	32.8	55	87	232	P
52.	34	31.7	18	35	164	A
53.	49	31.8	39	57	252	A
54.	38	30.8	16	25	184	A
55.	43	30.7	49	87	285	P
56.	56	31.5	111	85	251	P
57.	69	32.6	23	27	256	A
58.	54	30	58	94	275	A
59.	39	32.7	85	79	282	P
60.	42	32	50	43	240	P

*** P- FATTY LIVER PRESENT **A- FATTY LIVER ABSENT**

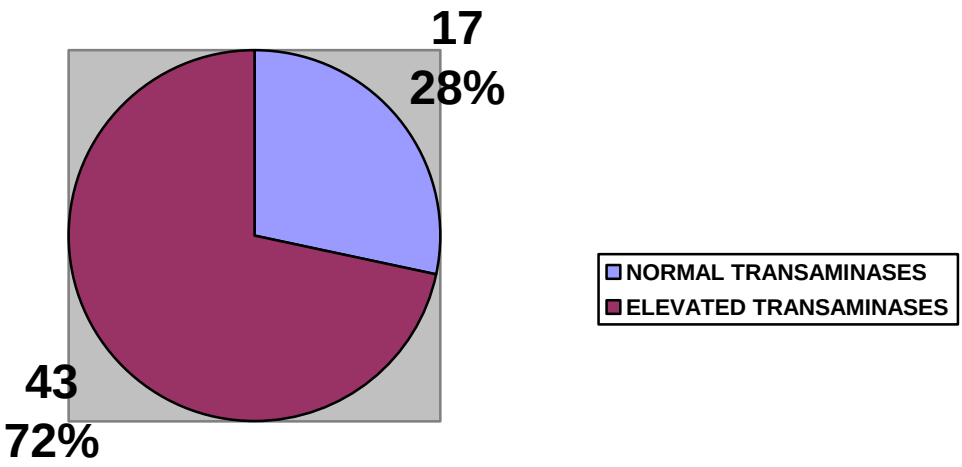
DISCUSSION ;

Between August 2006 and August 2008, 60 women subjects who attended the " MASTER HEALTH CHECK UP" were identified and included in this study. Only women were included, primarily because to rule out, the influence of alcohol for the changes in Sr. Transaminases, since very few women consume alcohol in our country. All the subjects who attended the " MASTER HEALTH CHECK UP" were asymptomatic and just routinely came for check up programs.

Sr. Transaminases were estimated using International Federation of Clinical Chemistry (IFCC).

DATA ANALYSIS

Of the total subjects 60, the number of subjects with elevated Serum Transaminases were totally 43.



Out of the 43 subjects who had elevated Transaminases, both Sr. AST and Sr. ALT were elevated in 38 subjects. Only Sr. AST was elevated in 1 subject. Only Sr. ALT was elevated in 4 subjects.

Of the 60 women, 39 subjects had Fatty Liver in Ultrasonography of the abdomen, and 38 out of 60 subjects had dyslipidemia.

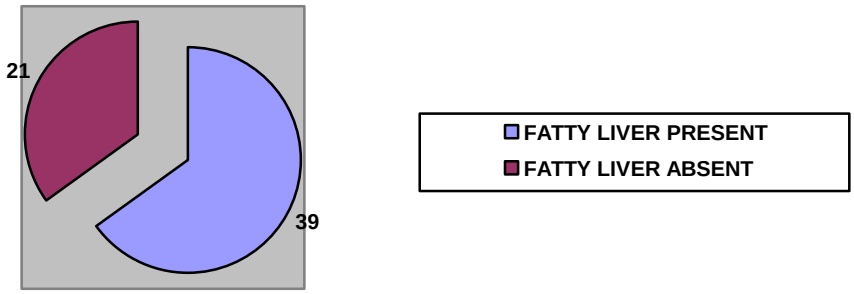


Figure 1: NO OF SUBJECTS WITH FATTY LIVER IN THE STUDY POPULATION.

Figure 2: NO OF SUBJECTS WITH DYSLIPIDEMIA IN THE STUDY POPULATION.

The total number of subjects with Fatty liver amongst the subjects with elevated Sr. Transaminase levels were 35. Only 9 subjects with elevated Sr. Transaminases did not show Fatty liver in Ultrasonography of the abdomen.

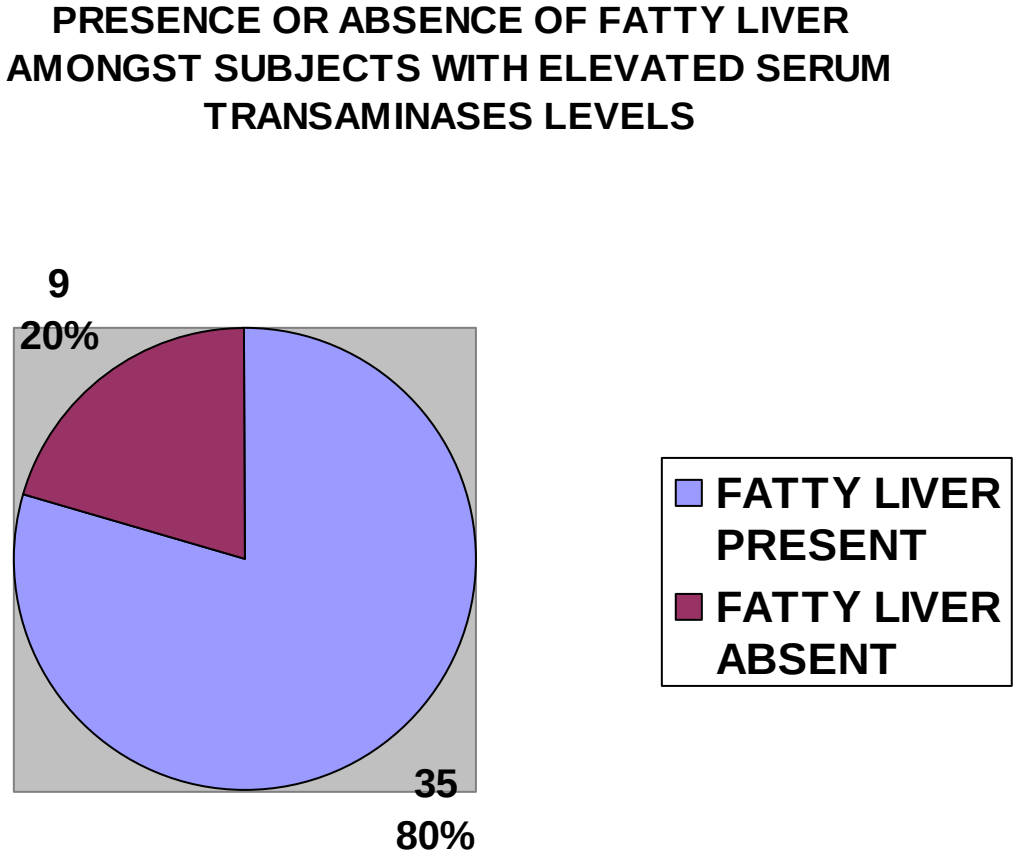


Figure 3: NO OF SUBJECTS WITH FATTY LIVER AMONGST THE 43 SUBJECTS WITH ELEVATED SR. TRANSAMINASES.

Most of the patients with elevated Sr. Transaminase levels had Dyslipidemia. Only 10 subjects had a normal Total cholesterol level as compared to the 33 subjects who had Dyslipidemia.

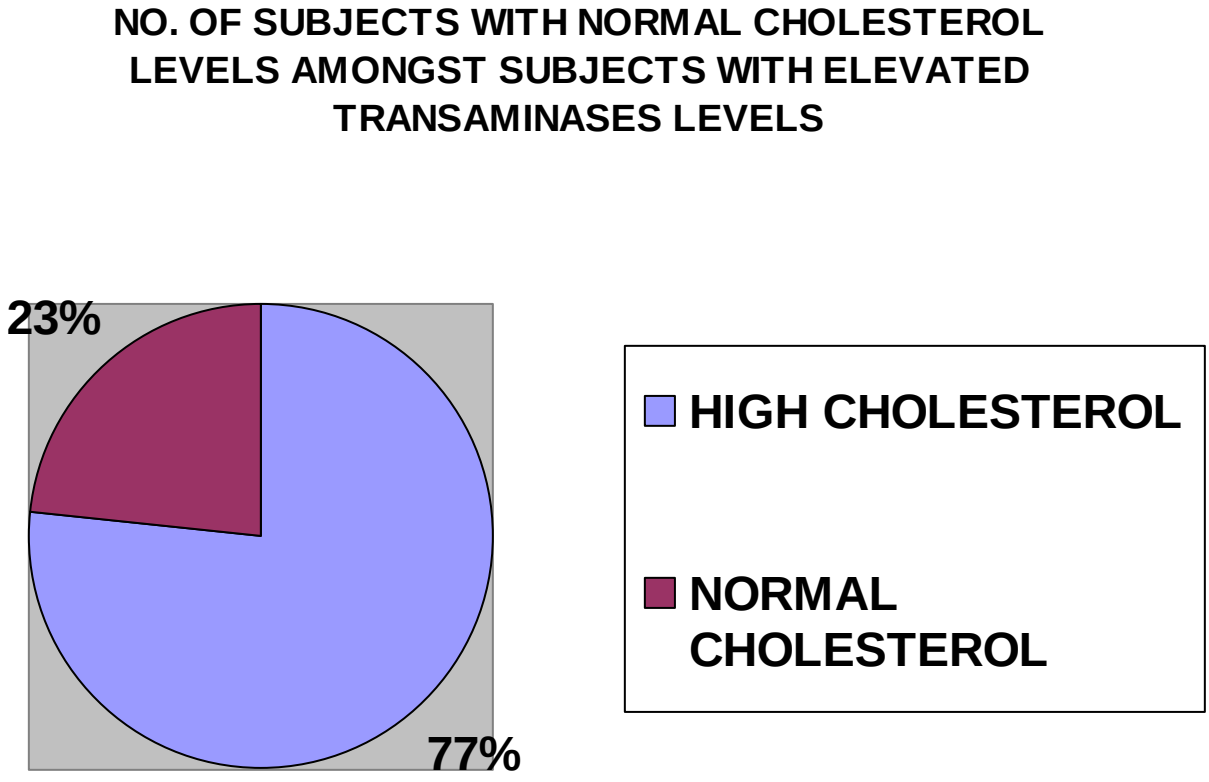


Figure 4: NO OF SUBJECTS WITH NORMAL CHOLESTEROL AMONGST THE 43 WITH ELEVATED TRANSAMINASES.

42 subjects out of the 43 subjects with elevated Transaminases, had either Fatty liver or Dyslipidemia. Only one subject did not have neither Fatty liver nor Dyslipidemia.

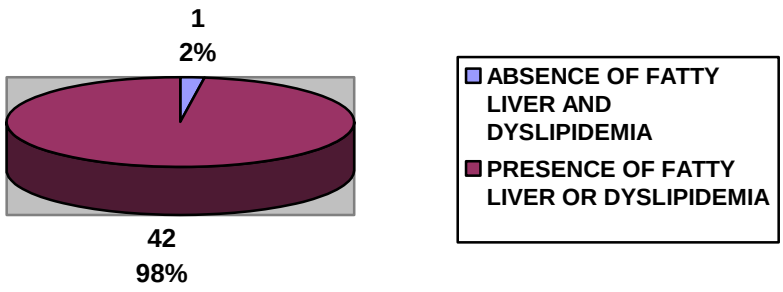


Figure 5: NO OF SUBJECTS WITHOUT FATTY LIVER OR DYSLIPIDEMIA AMONG THE 43 SUBJECTS WITH ELEVATED SR. TRANSAMINASES.

These figures show that, the presence of elevated transaminases in the absence of Fatty Liver or Dyslipidemia is negligible (only 1 subject). Sr. Transaminases are elevated only in the presence of Fatty liver or Dyslipidemia. Hence in our study, there is no direct correlation between BMI (obesity) and Sr. Transaminases levels. Sr. Transaminases are elevated only in the presence of Fatty liver or Dyslipidemia.

Descriptive statistical study for the correlation between BMI, and Sr. AST and Sr. ALT was done, both in the presence and absence of Fatty liver in ultrasonography.

There is not much correlation between BMI, and Sr. AST and Sr. ALT irrespective of whether fatty liver is present or not. The correlation values in both the cases varied between 0.1 and 0.3.

A "student's t-test" was applied to show whether there is variation in Sr. AST and Sr. ALT values in the presence or absence of Fatty Liver.

	Fatty liver	N	Mean	Standard Deviation	t	Signifi-cance
AST	PRESENT	39	56.4615	22.0381	4.267	**
	ABSENT	21	32.3810	18.3806		
ALT	PRESENT	39	62.4615	26.0251	3.987	**
	ABSENT	21	37.0000	18.1052		

The 't' values show that there is a significant difference in the Sr. AST and Sr. ALT values at P < 0.01 level when Fatty Liver is present.The mean Sr. AST and Sr. ALT in the *presence* of Fatty Liver were 56.46 and 62.46 respectively, and the mean Sr. AST and Sr. ALT in the *absence* of Fatty liver were 32.38 and 37 respectively. The Sr. Transaminases are found to be elevated in subjects with Fatty Liver.

Many studies conducted in the past have compared the presence of Fatty liver and the levels of Serum Transaminases.

Daniel et al. in 1999 conducted a study in 81 asymptomatic patients with elevated liver enzymes, out of which 73 subjects had

Nonalcoholic Fatty liver disease(NAFLD) and 8 subjects had a normal Liver in Biopsy(73).

Sorbi et al. in 2000 conducted a study in 36 subjects with elevated Sr. Transaminases and found that 21 had NAFLD, 5 had PSC/PBC, 3 had autoimmune hepatitis, 3 had non-specific changes, 3 had normal liver and 1 subject had Porfyria cutanea tarda in liver biopsy(74).

In a study of 354 subjects, conducted by Skelly et al. in 2001, 235 subjects had NAFLD, 21 had a normal liver and rest of them had other liver diseases in Liver Biopsy(75).

In none of these studies BMI was directly correlated with Sr. Transaminases.

In one large study conducted by Ruhl E, James E et al., in adult participants (5724) in the third U.S. National Health and Nutrition Examination Survey between 1988-1994, subjects underwent anthropometric measures and phlebotomy after an overnight fast. Participants with excessive alcohol consumption, hepatitis B, hepatitis C, iron overload, or known diabetes were excluded. The results of this study concluded that, central adiposity, hyperleptinemia, and hyperinsulinemia were the major determinants of the association of overweight with elevated serum Sr. ALT activity and BMI is not directly

correlated with the Sr. ALT levels(76).

The results of these studies suggest that a liver biopsy is not mandatory in asymptomatic patients with an unexplained rise in Sr. AST or ALT, after a thorough non-invasive evaluation. Some of these persons were unnecessary

subjected to a liver biopsy, because of the absence of liver disease or the lack of immediate therapeutical benefit of the biopsy findings.

The probability to diagnose NAFLD is high and lifestyle changes may be implemented without histological proof. Liver biopsy findings may sometimes point to a diagnosis which was overlooked at the time of the initial evaluation. Given the possible serious complications of liver biopsy (mortality 0.01%), it should not be performed to make up for a poor initial approach. The risks and benefits of a liver biopsy in this setting should be carefully considered, as it only seldom alters management.

Nonalcoholic Fatty Liver disease is a reversible condition, mainly by life-style and diet modifications, if unchecked may progress to steatohepatitis, fibrosis and cirrhosis.

All these subjects who had a high Total cholesterol value were advised to undergo a complete Fasting Lipid Profile which includes LDL(low density lipoprotein), HDL (high density lipoprotein) and

triglycerides. Patients with dyslipidemia were started on lipid lowering agents accordingly. Other subjects were given diet councelling and advised to execise physically.

Why only certain obese people develop Nonalcoholic Fatty Liver Disease and others of the same BMI do not develop NAFLD, is not clear. Whether there is a genetic predisposition for the development, is not proven. There is an urgent need to conduct large population based studies in our Country from various ethnic and regional areas to understand the epidemiology of this increasingly common condition. Trends of the changes will provide health managers and policy makers the recipe for interventions.

NOTE: In our study, which was conducted between August 2006 and August 2008, we have included obese women with BMI ≥30 considering that, BMI ≥30 are obese according to the WHO standards. In November 2008, India has released its own BMI standards, specifically tailored for the Indian population. According to the Indian Revised BMI standards, BMI ≥23 are overweight and BMI ≥25 are Obese. Hence further epidemiological studies are required, considering the Indian Revised BMI standards and the evaluation of Nonalcoholic Fatty liver disease and Sr. Transaminases, including subjects falling under this new revised category.

SUMMARY AND CONCLUSION ;

In our study, which was conducted in an Indian population with obese, Nonalcoholic subjects,

- **BMI (Obesity) is not directly correlated with Serum Transaminases.**
- **Sr. Transaminases are elevated only in the presence of Fatty liver or Dyslipidemia.**
- **The mean Sr. AST and Sr. ALT values in subjects with Fatty liver were 56.46 and 62.46 respectively. Hence, there is a definite increase in Serum Transaminase levels in the presence of Fatty liver.**

Encouragingly, Nonalcoholic Fatty Liver Disease is a reversible condition, and suitable lifestyle changes usually result in regression of Fatty , although drug therapy has not been fully validated.

Future directions require determination of the 'critically elevated' Serum Transaminases threshold value, development of drugs that would specifically and safely decrease Fatty Liver and subsequently reduction in Transaminases and conduction of interventional trials (also including obese subjects according to the new Indian revised BMI standards), to study the influence of diet and life-style modifications on the levels of Serum Transaminases.

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